REVIEWS

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Methodological and regulatory aspects of pharmaceutical development of biological products

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The aim of the work was to conduct an analysis of the current state and current trends in the approval of drugs, as well as some aspects of the methodology for their development based on biological molecules and registration.

Materials and methods. The material for the analysis was taken from the abstract databases of PubMed, Google Scholar and e-library.ru. The search was carried out using publications for the period from 2008 to 2023, the keywords were as follows: "biologicals", "new drug approval", "drug authorization", "drug development", "biosimilar", taking into account various spellings.

Results. Over the past 15 years, scientists have been observing revolutionary trends and processes in the field of the drug development, especially biopharmaceuticals. Significant advances have been made in gene, immune and cell therapies, resulting in the approval of such drugs more than doubling over the past ten years. The development of biological drugs includes the identification and testing of molecular targets and requires a deep understanding of the structure and functioning of the polypeptides involved in the development of the effect. The features of these active pharmaceutical substances are a high molecular weight, a complex three-dimensional structure and a high immunogenic potential. Preclinical and clinical studies of biologics have unique challenges. Selecting appropriate animal species, understanding the immunogenicity, and assessing pharmacodynamics and toxicological properties require a multilevel, detailed approach. The article discusses the regulatory framework under which these drugs are registered, summarizing the guidelines provided by international organizations such as the International Council for Harmonization and various national agencies.

Conclusion. The analysis highlights the current advances and prospects in the development of biologics, highlighting their key role in future transformations in the treatment of rare diseases and oncology, approaching the era of personalized medicine. Monitoring the development directions and technological approaches, as well as the commitment to global methodological and regulatory aspects can become a catalyst in the development of the Russian pharmacology.

Keywords: biologics; biosimilars; biomolecules, regulation; development and registration; U.S. Food and Drug Administration

Abbreviations: ADA – anti-drug antibodies; EMA – European Medicines Agency; FDA – U.S. Food and Drug Administration (USA); GPCRs – G-protein coupled receptors; ICH – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, IPO – initial public offering (of company shares on the stock market); API – active pharmaceutical substance; DNA – desoxynucleic acid; R&D – research and development work; NMR – nuclear magnetic resonance.

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Методологические и регуляторные аспекты фармацевтической разработки биопрепаратов

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Цель. Провести анализ текущего состояния и актуальных тенденций в одобрении лекарственных препаратов, а также некоторых аспектов методологии их разработки на основе биологических молекул и регистрации.

Материалы и методы. Материал для анализа брали в реферативных базах PubMed, Google Scholar и e-library.ru. Поиск осуществляли по публикациям за период с 2008 по 2023 год, с использованием следующих ключевых слов: «biologicals», «new drug approval», «drug authorization», «drug development», «biosimilar», учитывали различные варианты их написания.

Результаты. Последние 15 лет ученые наблюдают за революционными тенденциями и процессами в области разработки лекарств, особенно биофармацевтических. Значительные успехи достигнуты в генной, иммунной и клеточной терапии, что привело к более чем удвоению одобрения подобных лекарств за последние десять лет. Разработка биологических препаратов включает идентификацию, проверку молекулярных мишеней, требует глубокого понимания строения и функционирования вовлеченных в развитие эффекта полипептидов. Особенностями этих активных фармацевтических субстанций являются высокая молекулярная масса, сложная трехмерная структура и высокий иммуногенный потенциал. Доклинические и клинические исследования биологических препаратов имеют уникальные особенности. Выбор соответствующих видов животных, понимание иммуногенности, оценка фармакодинамики и токсикологических свойств требуют многоуровневого, детализированного подхода. В статье обсуждается нормативно-правовая база, в соответствие с требованиями которой осуществляют регистрацию этих препаратов, кратко излагаются руководящие принципы, предоставленные международными организациями, такими как Международный совет по гармонизации и различными национальными агентствами.

Заключение. Проведенный анализ отмечает имеющиеся успехи и перспективы в области разработки биопрепаратов, подчеркивая их ключевую роль в будущих преобразованиях в области лечения редких и онкологических заболеваний, приближая эру персонализированной медицины. Отслеживание направлений разработки и технологические подходы, а также приверженность мировым методологическим и регуляторным аспектам может стать катализатором в развитии российской фармакологии.

Ключевые слова: биологические препараты; биоаналоги; биомолекулы; регулирование; разработка и регистрация; U.S. Food and Drug Administration

Список сокращений: ЛС – лекарственные средства; ADA – антилекарственные антитела; EMA – Европейское агентство по лекарственным средствам; FDA – Управление по контролю качества пищевых продуктов и лекарственных средств (США); GPCR – рецепторы, сопряженные с G-белком; ICH – Международный совет по гармонизации технических требований к регистрации лекарственных препаратов для медицинского применения; IPO – первичное размещение акций компании на фондовом рынке; АФС – активная фармацевтическая субстанция; ДНК – дезоксирибонуклеиновая кислота; НИОКР – научно-исследовательские и опытно-конструкторские работы; ЯМР – ядерный магнитный резонанс.

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INTRODUCTION

Over the past 15 years, experts in the field of natural sciences have observed a new round of epy evolution in the drug development field, sometimes driven by revolutionary events. The number of drugs developed annually has increased, and the period for their creation has become noticeably shorter, which is clearly seen in the example of the drugs used in oncology. Regulators have become more open, and the requirements for the registration of medicines have become more accessible and flexible. The investments in the research and development (R&D) in the field of pharmaceutical progress have become almost the largest in the industry, and the IPO procedure has become available even to companies with a small capitalization, which has significantly facilitated the attraction of financing and, accordingly, increased the number of participants, and therefore competition. The expansion of technology has greatly simplified not only the development and creation of drugs, but also made it possible to reduce the time required for drug research, significantly increasing their quality and information content [1, 2].

Over the past few decades, the humanity has made significant scientific progress, based on the fact that gene therapy [3, 4], immunotherapy [5, 6], and cell therapy [7] are the new frontiers of pharmacology. Along with the development of new drugs, the foundation of pharmacology in the next decade will be built on the rational combination therapy with the existing drugs. Repurposing of the known drugs is partly perceived as a solution to the problem of high failure rates, significant costs, and a slow pace of new drug discoveries [8–10].

A widespread introduction of human-centered approaches (a patient-centered model, a client focus, etc.) makes it possible to assert that in addition to the traditionally basic qualities required for drugs, such as safety and effectiveness, the properties that a patient expects – the total of qualities – will become increasingly important, determining the ease of administration, the availability and cost. At the same time, it can be noted that the current state of science and technology makes it possible to create more and more drugs for effective, but still extremely expensive therapy (the therapy of rare and previously incurable diseases) [11].

It is widely known that the pharmaceutical industry is one of the most important and fastest growing segments of the global market. The investments in this area can be called the basis for an effective prevention of overaccumulation of capital, since, on the one hand, the pharmaceutical development is often accompanied by the development of the scientific and technological sector, and on the other hand, it has great translational potential, since it is highly integrated with other areas. The development of drugs for the treatment of orphan or rare diseases is risky, since a reliable forecast of the achievement timing and the final result, is difficult to guarantee. Nevertheless, it is still a rapidly developing area: there has been a pronounced increase in such startups and investments in them, since the cost of success exceeds manifold the most daring expenses. The indicated circumstance (a large number of participants and the scale of investment), along with the effectiveness at the level of complete cure, made it possible for the development companies to explain the cost of the drug in amounts of more than six figures [12, 13].

Billions of dollars invested following IPOs of innovative companies, fuel scientific breakthroughs. The key areas include gene therapy, genome editing, cell therapy and the use of induced pluripotent stem cells. It is expected that these areas will remain important in the near future [14, 15]. Extensive funding for innovative projects from pharmaceutical companies, states and foundations contributes to a high competition among start-ups and the progressive development of technologies. Many of these technologies show the potential for an exponential growth with an unpredictable outcome.

In the field of creating new drugs, researchers have long identified a certain trend, the presence of which is largely explained by the above. It is known that all new drugs can be divided into the following ones: those containing small molecules or the drugs created on the basis of a biological approach. Herewith, until recently, a widespread use of biotechnology was limited by the level of technology development and costs, but almost all participants have agreed that biotechnology will sooner or later provide more opportunities for a pharmaceutical development than medicinal chemistry [16–18]. At the same time, the development of drugs based on chemical synthesis and medicinal chemistry as a science, have undergone and continue to undergo a number of significant changes. For example, the cost of synthesis and production is no longer such a significant factor, the influence of which determines the prospects of the idea. Rather, on the contrary – the more complex the synthesis and development is, the more promising the product idea looks, since this circumstance makes it possible for them to acquire additional guarantees of safety against the reproduction by other players, along with practice strategic patenting with the creation of a network of secondary patents, the practice of “artificial” extension of exclusive rights (“an evergreen patent”) [19, 20]. From this perspective, biological

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products also remain attractive for the investment. Over the past few years, there has been a colossal rise in the development of drugs using biotechnology methods: the number of drug approvals has more than doubled over 10 years (from 23% approved in 2013 to 54% in 2022) (Fig. 1).

This review is devoted to the analysis of the main trends, methodological and regulatory aspects of the pharmaceutical development of biologics.

THE AIM of the work was to analysis of the current state and trends in the approval of drugs, as well as some aspects of the methodology for their development based on biological molecules and registration.

MATERIALS AND METHODS

To collect the materials, the abstract databases of PubMed, Google Scholar and e-library.ru, as well as the official websites of the FDA and EMA were used. The search was carried out using the publications for the period from 2008 to 2023, the keywords were as follows: "biologicals", "new drug approval", "drug authorization", "drug development", "biosimilar", taking into account various spellings. The exclusion criteria comprised older publications and articles not directly addressing the topic of the review. 160 sources were analyzed and, after the systematization, articles by different authors containing similar information were removed. After screening, 50 sources were considered suitable for the inclusion in the review.

RESULTS AND DISCUSSION

Types of biologics

Historically, general approaches to the development of drugs were regularly revised, following the advances in related scientific fields, and new technologies, entering the practice of researchers, created the preconditions for the emergence of drugs that were fundamentally different from those that had existed previously. In particular, the improvement of organic synthesis methods has made it possible to move from the era of "accidental" discoveries of the drugs isolated from the natural sources to the targeted synthesis of small molecules, the creation of libraries of the substances for a subsequent screening of a biological activity, and also, in general, to the dominance of the "structure–activity" approach in relevant scientific works. The progress in the field of molecular biology and biotechnology, in turn, has opened the way to the widespread introduction into clinical practice of drugs, the production of which by chemical synthesis methods is either extremely expensive or fundamentally impossible due to the complexity of the molecular structure [23, 24].

Biological medicines (biologics) are a fairly heterogeneous group of drugs, the common feature of which is the production or isolation of their active substances from a biological source other than plants. Currently, according to the Decision of the Council of the Eurasian Economic Commission No. 89 dated November 3, 2016, "On approval of regulations of a biologics clinical trials of the Eurasian Economic Union"[1], biologics include:

– immunological (immunobiological) drugs, i.e., the drugs intended for the formation of active or passive immunity, or diagnostics of the presence of immunity, or diagnostics (development) of a specifically acquired change in the immunological response to allergenic substances;

– biotechnological medicinal products, i.e., the drugs produced using biotechnological processes and methods of the recombinant DNA technology, controlled expression of genes encoding the production of biologically active proteins, hybridoma technologies, monoclonal antibodies or other biotechnological processes;

– plasma-derived medicinal products;

– probiotic (eubiotic) medicines;

– phage preparations;

– high-tech drugs: gene therapy drugs, the drugs based on somatic cells, tissue-engineered medicinal products (tissue engineering drugs);

– medicinal products containing the following active pharmaceutical ingredients (APIs): non-recombinant origin, produced or isolated from biological sources (human tissues, fluids and organs, raw materials of the animal origin, microorganisms or their metabolic products), with the exception of antibiotics.

The idea of using active substances of the animal origin as drugs is not new, and a number of drugs, for example, vaccines, unfractionated heparin, lysozyme, insulin, pancreatin, thyroxine, vitamin D, etc., have an experience of their use that is comparable to the experience of using the earliest modern drugs obtained by chemical synthesis, or even longer. In particular, the first mentions of the variolation practice date back to the 7th century, and the first vaccines appeared in the 18th century, which makes it possible to consider the history of vaccines to be longer than, for example, the history of the appearance of local anesthetics and non-steroidal anti-inflammatory drugs, which appeared at the end of the 19th century (e.g., tetanus serum) [25, 26].

[1] Decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 89 "On approval of the Rules for conducting research on biological medicinal products of the Eurasian Economic Union." Council of the Eurasian Economic Commission. Available from: http://docs.cntd.ru/document/456026116. Russian

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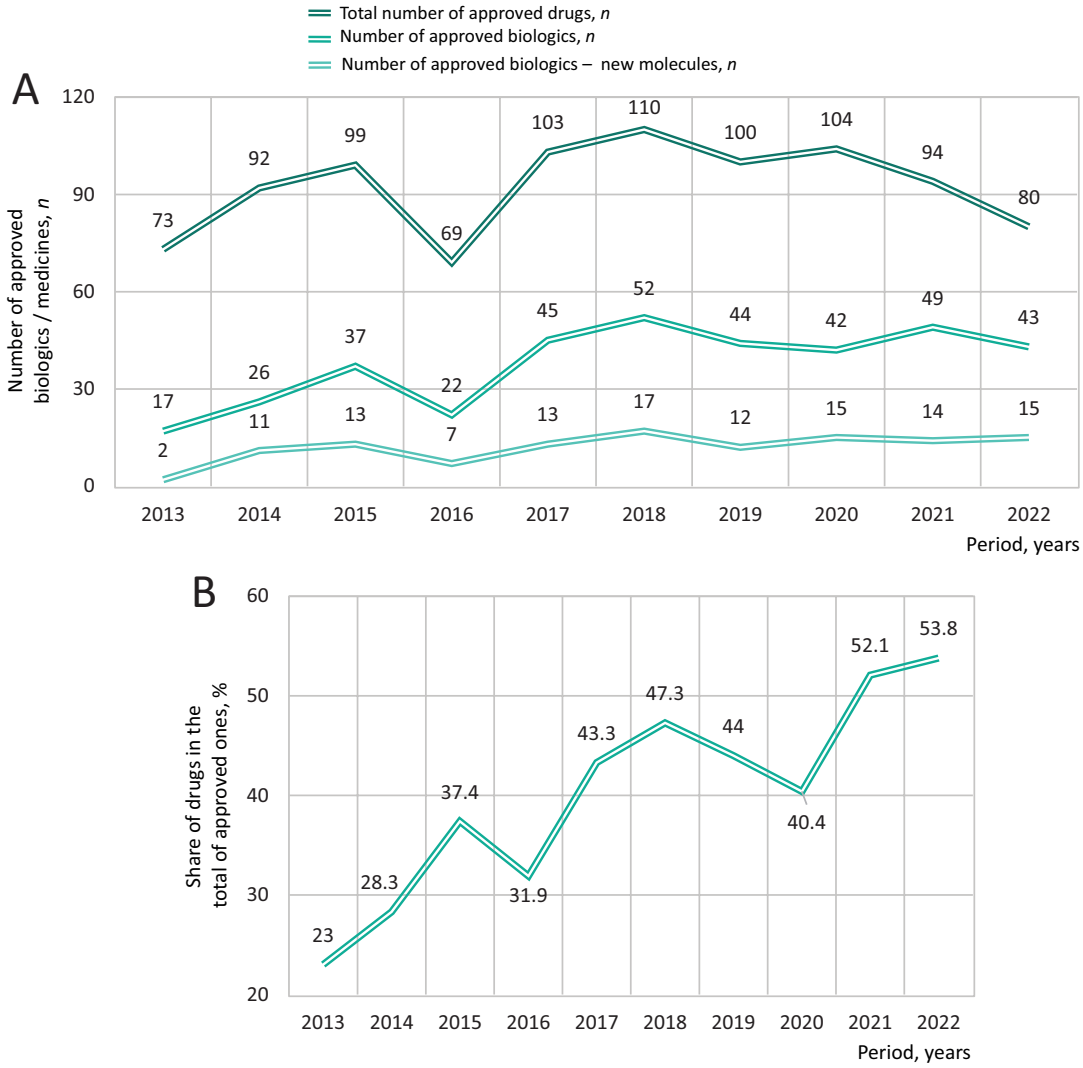

Figure 1 – Number of FDA-approved drugs – new molecular compounds and biologics for the period from 2013 to 2022

Note: FDA – U. S. Food and Drug Administration. The presented graphs are adapted from [21, 22].

1	**Selection of conventional animal species**					
	Mice		Rats	Rabbits	Dogs	Non-human primates
2	**Assessment of molecular biological characteristics**					
	Amino acid sequence identity		Expression	Binding and affinity	Effect size	Presence of secondary targets
3	**Availability of a relevant species (with matching characteristics)**					
	Yes			No		
	Conducting research on 1 species of rodents and 1 species of non-rodents	or	Conducting research on one animal species	Selection of "surrogate" species for assessing individual effects	Use of transgenic models	Use of *in vitro* data

Figure 2 – Scheme for selecting relevant animal species for pharmacodynamic studies

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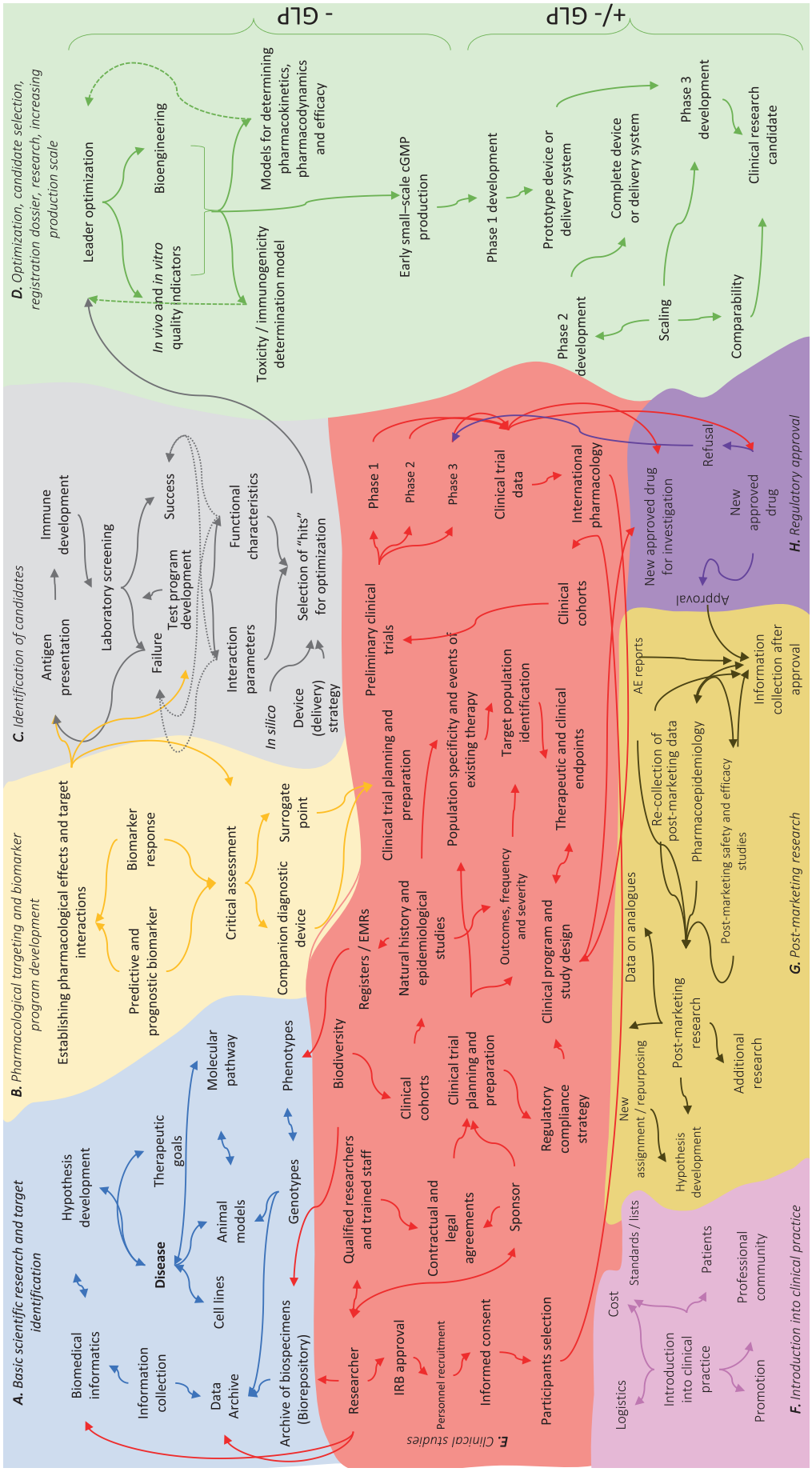

Figure 3 – Generalized scheme for biological drug development

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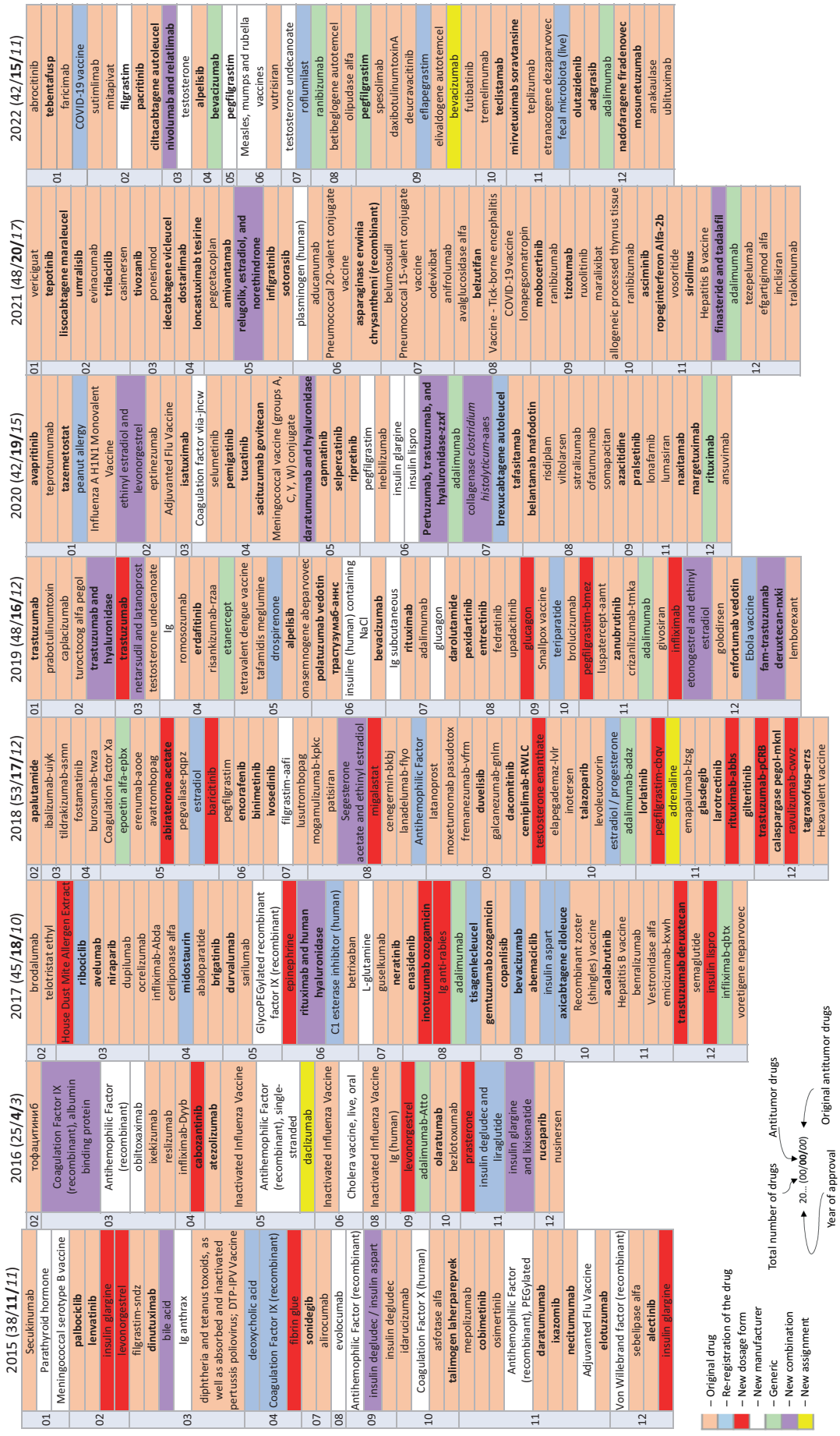

Figure 4 – List of biopharmaceutical drugs approved by the FDA from 2015 to 2022

Note: the numbers indicate the year (horizontally) or month (vertically) of approval, the total number of drugs, the number of approved drugs for the treatment of oncological diseases is highlighted in bold, the number of original drugs used for oncological diseases is indicated in italics. The meaning of the color indicators is shown in the figure.

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Development and validation of molecular targets

Currently, the most rapidly developing segment in the field of biologic is the development of biotechnological drugs, the pioneer in which was Eli Lilly (India). It first mastered the production of recombinant insulin (humulin) in 1982. This technology is based on the use of "the reverse engineering", which, to one degree or another, is applicable to the development of any modern biotechnological drug. After studying the molecular aspects of the disease pathogenesis, it becomes possible to identify the substances which deficiency (for example, a deficiency of certain enzymes in fermentopathies) or excess (for example, an excess of cytokines in rheumatological diseases) plays a key role in the progression of the disease [27, 28]. In order to sufficiently characterize a potential target, a combination of many methods from various fields of science is used: structural biology (an X-ray diffraction analysis, NMR, cryoelectron microscopy) – to identify functional areas and binding sites of biomolecules; molecular biology and genetics (nucleic acid sequencing) – to search for pronounced relationships between genotype and phenotype; proteomic technologies (mass spectrometry, chromatography, two-dimensional electrophoresis) – to compare proteomic maps obtained from healthy individuals and pathologies; fluorescence microscopy – to identify the intracellular location of individual proteins and their colocalization with other proteins; computational biology – for modeling the structure and dynamics of biomolecules *in silico*, i.e., without carrying out labor-intensive experiments [29–32]. At the next stage, it is necessary to validate the found target, i.e., to confirm its significance for the development of the disease using an adequate experimental model and identify key markers that can be used for a subsequent assessment of the disease severity [33–35].

As a rule, the targets for drugs are polypeptides that have their own functional activity: hormones, receptors, transport proteins and enzymes. According to various estimates, the currently used drugs collectively target up to 400 different proteins, and at least 700 more proteins have been identified using bioinformatics approaches. There are relatively few targets for the molecules produced by chemical synthesis: in particular, the study of the functional characteristics and intracellular cascades of G-protein coupled receptors (GPCRs) has become the basis for the development of approximately one third of existing drugs. Transport proteins (ion channels) and enzymes are the targets of 29 and 15% of the existing drugs [36, 37].

If replacement therapy is necessary, the developer's task becomes quite simple: to reproduce a polypeptide that does not function properly in a patient's body. According to this logic, not only insulins of various classes but also a number of other drugs, for example, idursulfase, an enzyme intended for the replacement therapy in patients with mucopolysaccharidosis type II (Hunter syndrome), were developed. At the same time, the structure-activity principle is also applicable in the field of biologics. In particular, it is illustrated by a whole class of monoclonal antibody drugs, the examples of which are both enzyme inhibitors (imatinib) and blockers of certain cytokines (infliximab, adalimumab, dupilumab), which are widely used in the treatment of oncological and autoimmune diseases. Fundamentally, in such cases, biological products, having a higher molecular weight, have advantages over small molecules, since they are able of highly and specifically contacting larger structures, incl. even with such complex targets as soluble proteins [38, 39].

Preclinical and clinical studies

The role of preclinical research in the development of biological products is controversial, since much will depend on the balance between the sensitivity of the experimental model and the ability to extrapolate the experimental results to the clinical characteristics of the drug. In particular, *in vitro* studies will be inferior in importance to *in vivo* tests for predicting clinical characteristics. However, having a sufficient reproducibility and the highest sensitivity to changes in the molecular structure of the API, they become an indispensable tool for monitoring the quality of the finished product. The opportunities for *in vivo* studies depend on the availability of a suitable experimental model that is relevant to humans and takes into account possible pleiotropic effects, species-specifity and immunogenicity of the drug under study, and also makes a sufficient assessment of "dose-response" and "plasma concentration-response" relationships possible. For example, any species of laboratory animals can be suitable for assessing the pharmacological effects of biological molecules with a sufficiently high degree of conservation (insulin and other peptide hormones), while non-human primates[2] become the species of choice for studies of monoclonal antibody preparations.

[2] Ibid.

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PHARMACY & PHARMACOLOGY

As a rule, a relevant species is understood as the animals in which a drug exhibits its appropriate pharmacological activity due to the interaction with a receptor, an active site or epitope of a particular protein, therefore, to search for relevant species, various methods including immunochemical and functional tests necessary to assess distribution targets in tissue, are used. In particular, in monoclonal antibody studies, the relevant species are the animals that have an expression of the desired epitope and a similar tissue cross-reactivity profile (when compared to human tissues). Another significant aspect of choice is the potential immunogenicity of biological molecules, especially therapeutic proteins. Immunogenicity can lead not only to severe, potentially fatal adverse reactions (an anaphylactic shock, a cytokine storm), but also to a decrease in the effectiveness of the drug due to the appearance of antidrug antibodies (ADAs), able of blocking the binding of the drug to the target or changing the rate of its elimination from the body. The immunogenic potential of a biologic is influenced by its source and structural features: for example, highly immunogenic murine antibodies have been successively replaced with chimeric, humanized, and fully human antibodies to reduce the likelihood of the ADAs production in humans, but such modifications may result in greater immunogenicity in animals. Therefore, for the correct interpretation of the research results with multiple dosing, it becomes important to assess the humoral immune response to the administration of the drug under study: for example, the antibody titer, the number of the animals in which the antibody production was recorded, the properties of the induced antibodies (a neutralizing activity or lack thereof), as well as its correlation with changes in pharmacological and/or toxic properties. Detection of antibodies in animals does not allow predicting the development of an immune response in humans, and therefore, this phenomenon should not act as the only reason for an early termination of preclinical studies or changes in their duration, except the cases where the development of an immune response is the reason for modifying the effects of the drug in a significant proportion of animals [40, 41].

A multilevel approach should be taken to select relevant laboratory animal species, taking into account both the availability of relevant targets and the potential immunogenicity profile that may influence the results of repeated-dose studies (Fig. 2).

At the first stage, the identity of the target should be assessed at the level of the amino acid sequence; at the next stage, the expression of the target, as well as the presence of similar ligands and receptor signaling pathways in target tissues and non-target tissues, incl. the possible cross-reactivity, should be also assessed. Next, it is necessary to assess the characteristics of the target comparability between the animal species and humans, which is usually carried out during *in vitro* studies necessary to assess the binding affinity, the activity and pharmacodynamic response at both cellular and organismic levels. In the absence of relevant biological species and/or with a proper justification, it is permissible to use alternative approaches: using homologous molecules instead of the target API, using humanized (including transgenic) animals, or using exclusively *in vitro* data (not applicable to justify the lack of toxicological studies)[3].

In toxicological studies, on the contrary, the use of homologs is not allowed, since the final product in them (usually already in the finished dosage form, which is intended to be used in clinical trials) is subject to testing. The selection of species for toxicological studies is generally based on the same principles as for the pharmacodynamic studies, herewith, it is necessary that toxicological studies should be conducted on at least one species in which the pharmacological activity has been demonstrated. At the same time, the requirements for the toxicological studies of a biological product can be called less stringent than those for the studies of small molecules: mutagenicity and carcinogenicity studies are not required, while the need for reproductive toxicity studies is determined depending on the properties of the drug, planned indications for the us, and characteristics of the target patient population [42, 43].

However, even the selection of the most relevant model cannot guarantee the success of clinical studies: on the one hand, this is due to the impossibility of obtaining adequate data on the immunogenicity of human or humanized proteins in humans, and on the other hand, it is due to the interspecies differences in the structure and/or expression of certain proteins. In particular, there is a sad example of a phase I study failure of teralizumab (TGN1412), a humanized monoclonal antibody intended for the treatment of B-cell chronic lymphocytic leukemia and rheumatoid arthritis in 2006. The administration of the drug at a dose that was 500 times lower than that recognized as safe in animals,

[3] Ibid.

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provoked a cytokine release syndrome in the volunteers. That was due to the absence of the CD28 molecules expression, which were the target of teralizumab, on the $CD4^+$ lymphocytes of cynomolgus monkeys used in preclinical safety studies [44, 45]. Notably, in the 2016 study performed on humanized mice, the ability of teralizumab to cause a cytokine release syndrome, a white blood cell destruction, and other adverse effects was also confirmed [46]. Although this precedent has led to a more wary attitude towards the studies of biological products, the general principle of conducting phases I–III does studies not differ significantly from that when conducting studies of drugs containing APIs obtained by chemical synthesis methods. In all the cases, the essence of the tests is reduced to a consistent assessment of safety, the relationship between pharmacokinetics and pharmacodynamics, a selection of the optimal dose for the target indications for the use and confirmation of the clinical significance of the observed manifestations with an assessment of the overall effectiveness and safety. The only fundamental difference is the mandatory inclusion in the clinical development program of any biotechnological drug (including biosimilars) of immunogenicity assessment (clinically significant cases of the antibody titers formation and the maintenance of their titres for a certain time), incl. the post-registration period[4].

Active pharmaceutical substances of biological origin

A quality control of biological products is required to confirm the continuity between each of the successive stages of its development described above. The quality assurance and quality control for biotechnology products is more complex than for small molecules, due to both the greater complexity of the chemical structure and the manufacturing processes involved. As a rule, the production of biological products, in comparison with the drugs from the group of so-called small molecules, is longer, requires more raw materials and is characterized by a significantly larger number of critical technological stages that require taking into account a greater number of factors when predicting possible risks[5].

The key features of biological APIs are a high molecular weight, a complex three-dimensional structure (incl. due to the presence of tertiary / quaternary structure, a certain ratio of isoforms, high heterogeneity, as well as glycosylation processes), uniqueness of starting materials (incl. the used cell lines and viral vectors), a high sensitivity to storage conditions and thermolability, as well as a high immunogenicity potential. The above dictates special requirements for the organization and quality of the production of preclinical and clinical studies of APIs of biotechnological origin at all stages, since even minor changes in the production process (including the ones during scaling or transfer) can significantly effect not only on the profile of impurities in the API, but also on its structure and, therefore, on its possible effectiveness and safety. Therefore, in the documents regulating the development and registration of biological products, special attention is paid to comparability studies: the confirmation of the absence of clinically significant differences between biological products after changes in the production technology relative to a biological drug produced using an unchanged technology. For the drugs containing APIs obtained by chemical synthesis methods, such confirmations, as a rule, are reduced to an analysis of the identity / comparability of finished dosage forms. The studies are carried out according to the indicators stated in the specification, and in some cases, the results of a comparative dissolution kinetics test or a clinical bioequivalence study may be required. These tests are aimed at confirming the comparability of the release and absorption rate of the API from the finished dosage form, which, if successful, makes it possible to fully extrapolate the previously obtained information about the effectiveness and safety of the finished drug to its updated version[6]. In the vast majority of cases, biotechnological drugs are aqueous solutions at the time of administration. In the case of the APIs obtained by chemical synthesis, such a dosage form would completely avoid bioequivalence studies. However, to confirm their comparability, a whole range of tests will be required, which is especially important for the development of biosimilar drugs – the biological products containing a version of the active substance of the registered original (reference) biological product, for which similarity has been demonstrated on the basis of comparative studies in terms of quality, biological activity, efficiency and safety. It is also important to note that the choice of methods for studying and/or confirming the declared physicochemical, biological and clinical characteristics of a biological product is determined not only by current guidelines and/or recommendations, but also by the general level of scientific knowledge. The applicability of

[4] Ibid.
[5] Ibid.
[6] Ibid.

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Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

a biosimilarity approach to a particular biologic depends on the availability of modern analytical methods, the manufacturing processes used, and the availability of clinical models to assess their comparability[7].

The existing guidelines from The International Council for Harmonization (ICH)[8], which underlie regulatory requirements for the development of drugs, include separate guidelines that apply exclusively to biological products (for example, the guidelines for a preclinical safety assessment of biotechnological Medicines (S6(R1))[9], the guidelines for viral safety (Q5A)[10], the analysis of expression constructs (Q5B)[11], the assessment of the resulting product stability (Q5C)[12], the characterization of the cell lines used (Q5D)[13], checking the products comparability when changing the production process (Q5E)[14], and separate guidance on preparing specifications for biologics (Q6B))[15]. Regulatory agencies also publish their own guidance on specific subgroups of biological agents; i.e., the European Medicines Agency (EMA) has published more than 40 guidelines, the vast majority of which are also devoted to the aspects of the biological products quality: the methods of expressing activity when indicating dosage, characterization of vector constructs used, drawing up specifications for monoclonal antibodies, a manufacturing process validation, a quality control of biological products individual groups (vaccines, the products obtained from human blood plasma, gene therapy agents, etc.), as well as a number of other private guidelines[16].

Biologics, unlike small molecules, do not have a complete relationship between structural and functional properties, and analytical methods do not makes it possible to fully study all the parameters significant for safety and effectiveness. That is why "classical" specifications (with indicators such as description, quantitative definition, microbiological purity, related impurities, etc.) function as less universal tools in quality assurance. The main parameters of biotechnological products are authenticity, purity, immunogenicity, biological activity and stability[17].

To determine the authenticity, a thorough study of physicochemical properties is carried out. Herewith, a combination of various analytical methods are used, e.g., colorimetric methods – to determine the total protein concentration, an enzyme-linked immunosorbent assay – to confirm an immunochemical authenticity; chromatographic methods, electrophoresis and various types of blotting – to determine a molecular weight; a profile of charged variants, a profile of post-translational modifications, etc., mass spectrometry – to determine the molecular weight, a glycosylation profile, a correct formation of disulfide bonds, as well as N- and C-terminal sequencing in combination with peptide mapping – to determine the primary peptide sequences. Herewith, the authenticity must be determined at all stages of the pharmaceutical development, including both for a routine control of batches during the commercial production and at the stages of preclinical studies[18].

The purity requirements[19] for a biological product differ from those for small molecules, since impurities in them can be either variants of the target product or manufacturing impurities. A complete removal of impurities is usually impossible, so they must be characterized in terms of their impact on the efficacy and safety profile of the drug. Most often, a combination of several methods is used to control the purity of biological products: size exclusion chromatography (to determine aggregates and possible degradation products), capillary electrophoresis (to determine the products of a chemical modification of the protein and low molecular weight products of its degradation), peptide mapping (to identify changes in amino acid

[7] Ibid.
[8] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Official web site. Available from: https://www.ich.org/
[9] ICH Harmonised Tripartite Guideline. S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (2011). Available from: https://database.ich.org/sites/default/files/S6_R1_Guideline_0.pdf
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[16] Biological Guidelines | European Medicines Agency. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/biological-guidelines
[17] Decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 89 "On approval of the Rules for conducting research on biological medicinal products of the Eurasian Economic Union." Council of the Eurasian Economic Commission.
[18] Ibid.
[19] Ibid.

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compositions), chromatography high resolution (for determining other protein and low molecular weight impurities).

A virus safety[20] is ensured by checking source materials for the presence of viruses, validating the production process in terms of the impact on the number of viral particles, and by testing products at different production stages for the presence of viruses.

An immunogenicity[21], which refers to the ability of a drug to induce an immune response, most often occurs when using therapeutic proteins. Various post-translational modifications can have a significant impact on the immunogenicity of proteins, including a glycosylation, an aggregate formation and chemical modifications, the controls of which are assessed to determine the identity and purity. At the same time, methods for detecting ADA (usually using an enzyme-linked immunosorbent assay) and assessing their neutralizing activity against drugs should be also included in the specification for biotechnological drugs.

A biological activity[22] is a key indicator of a biological product quality, as it correlates with its clinical effectiveness. As a rule, several methods are used, but all of them, one way or another, must be carried out in living systems – cells and tissue cultures *in vitro* or on laboratory animals *in vivo*. Obviously, the results of such tests can be variable, so, the development of suitable methods that can ensure the reliability, reproducibility and accuracy of measurement results, begins with the development of the drug, incl. during preclinical studies, and may continue until the start of phase III clinical trials (Fig. 3).

As noted above, biologics can be sensitive to light, a mechanical stress, and temperature fluctuations, so, stability testing differs from that performed for small molecules. In particular, the results of an accelerated stability[23] experiment cannot be extrapolated to a longer shelf life, so, the registration will require stability data for the entire expected shelf life under real-world conditions. Assessing the stability of biological products will necessarily include the assessment of identity, purity (especially degradation products) and a biological activity for a minimum of 6 months.

Biologics approved by FDA from 2015 to 2022

For the period from 2015 to 2022, the FDA has approved the use of 341 biotechnologically created drugs, 120 of them are aimed at treating cancer, 91 are original molecules (Fig. 4). This indicates that, on the one hand, the problem of the spread of cancer continues to be a serious threat, the search and development of means to combat it have a sufficient funding, and on the other hand, it indicates significant advances in the field of fundamental ideas about the pathogenesis of the disease and progress in the field management technologies. Analyzing the number of drug approvals in a year-based way, it can be concluded that they are evenly distributed with a clear tendency towards a gradual increase. The approved drugs are mainly represented by original products (230 in number), 92 of which are drugs for the treatment of oncological diseases, 25 are represented by new dosage forms (for 2020, 2021 and 2022 there were no approvals related to the registration of drugs in a new dosage form), 14 are generics, 3 of which relate to the drugs for the treatment of oncological diseases, 3 drugs were approved due to the introduction of a new indication for use, 22 – due to the re-registration, 28 – due to a change of the manufacturer and 17 drugs were approved as new combinations, 8 of which are used in the treatment of cancer. Analyzing these data, the following conclusion can drawn: the data confirm the statement about the steady growth of the pharmaceutical market, the main driver of which is original drugs, new combinations and dosage forms, as well as the expansion of indications for the use of already known drugs [47–50].

CONCLUSION

Modern biologics developed by reverse engineering methods represent the apogee of the development of the structure-activity approach previously used in the development of small molecules. Biotechnological drugs can provide indispensable tools for targeted and personalized therapy, but their development is complicated by the need for a careful selection of relevant biological species and experimental models used not only in preclinical studies, but also for a routine quality control of finished products. The quality control of biological products is the most significant aspect of their development. The analysis highlights current advances and prospects in the development of biologics, highlighting their key role in the future transformations in the treatment of rare diseases and oncology, ushering in the era of personalized medicine. Monitoring development directions and technological approaches, as well as commitment to global methodological and regulatory aspects, can become a catalyst in the development of Russian pharmacology.

[20] Ibid.
[21] Ibid.
[22] Ibid.
[23] Ibid.

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Scientific and Practical Journal
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All authors confirm that their authorship meets the international ICMJE criteria
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